PERSPECTIVES

Male and female equality: still far from goal

Liliana Sintra Grilo[1,2]
and Hugues Abriel[1,3]
[1] *Department of Pharmacology and Toxicology, University of Lausanne, Switzerland*
[2] *Pharmacochemistry, School of Pharmaceutical Sciences, University of Lausanne, University of Geneva, Switzerland*
[3] *Service of Cardiology, CHUV, Lausanne, Switzerland*

Email: hugues.abriel@unil.ch

It is well established that the cardiac electrophysiological properties of males and females are not equal. In particular, the ventricular repolarization of the female heart is characterized by a longer rate-corrected QT interval (QTc) of the electrocardiogram (ECG, see Fig. 1). This may be the reason why females are more prone to develop polymorphic ventricular tachyarrhythmias, called Torsades de Pointes (TdP), that occur when the ventricular repolarization is further delayed by intrinsic or external factors (Fig. 1) (Abi-Gerges *et al.* 2004). TdP may lead to syncope or to sudden cardiac death.

The concept of *repolarization reserve* was proposed a few years ago by Dr Roden to help predict one's risk of developing TdP (Roden, 1998). It has been suggested that, in a normal heart, rapid and orderly repolarization occurs thanks to the coordinated activation of different voltage-gated potassium channels. Several factors may reduce this repolarization reserve and make it more likely to precipitate TdP in at-risk patients. Hypokalaemia and cardiac diseases, e.g. congenital long QT syndrome (LQTS), are known to decrease the repolarization reserve, as well as treatment with drugs blocking potassium channels. It is important to note that women present an initially reduced repolarization reserve (Roden, 1998).

The potassium channel hERG (human *ether-à-go-go-related gene* channel) is under the spotlight since the discovery that many drugs may block it, and, as a consequence, the I_{Kr} current it generates. I_{Kr} is the rapidly activating delayed rectifier potassium current which plays a primary role for ventricular repolarization in humans and thus action potential duration (APD) and QTc (Fig. 1). This adverse effect of drugs, also referred as *drug-induced* LQTS (di-LQTS), should be considered as an iatrogenic channelopathy (Abriel *et al.* 2004), and, again in this case, males and females are not equal. Incidence of TdP under prescription of hERG-blocking drugs is about 60% more common in females than males (Abi-Gerges *et al.* 2004).

In an observational study (Rautaharju *et al.* 1992) investigating the sex differences of the QT interval, a 20-ms QTc shortening was observed after puberty in males, whereas female values remained unchanged throughout growth and reproductive years. Since this difference is absent before puberty, sex hormones were naturally hypothesized to play a role. The question of whether QTc is influenced by the menstrual cycle or in postmenopausal women under hormone therapy is controversial. A few studies reported no difference (Burke *et al.* 1997; Larsen *et al.* 1998), whereas others observed slight, but significant, QTc prolongation consistent with hERG inhibition by oestrogen (Rodriguez *et al.* 2001; Kadish *et al.* 2004). Moreover, removal of the ovaries in female rabbits shortened the QT interval, while hormone replacement using 17β-oestradiol (E2) lengthened it (Drici *et al.* 1996).

In this issue of *The Journal of Physiology*, Kurokawa *et al.* (2008) postulate that E2 may

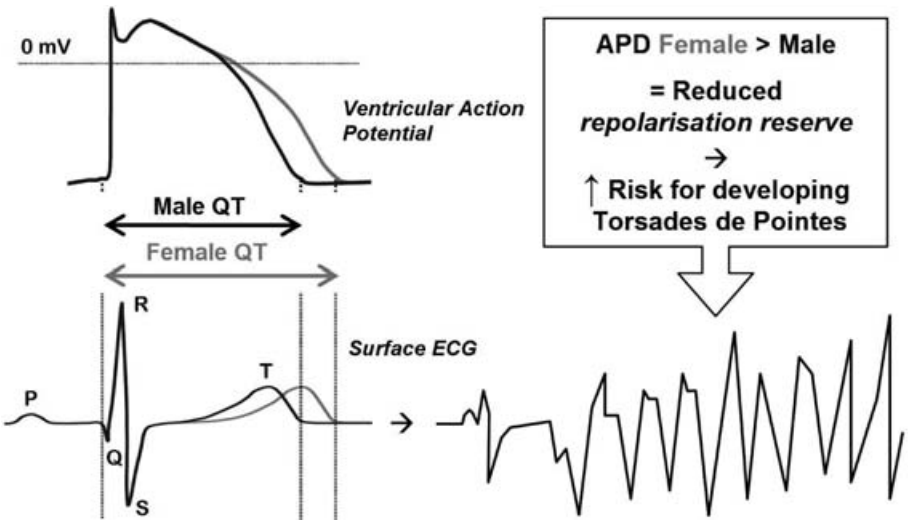

Figure 1. Scheme illustrating the ventricular action potential and surface electrocardiogram (ECG)
The QT interval – time between start of the QRS complex and end of T wave – reflects, in part, the action potential duration (APD). Females have a longer APD and QT interval than males. The *repolarization reserve* of females is smaller; hence, they are at higher risk for Torsades de Pointes when exposed to factors such as drugs blocking the hERG channel delaying further the repolarization.

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also acutely modulate the hERG-mediated current via a non-genomic pathway. In this comprehensive study, the authors first showed a bi-phasic effect of E2 on the QT interval from Langendorff-perfused guinea pig hearts. Using high physiological concentrations of E2 (1 nM), QTc intervals were significantly prolonged, whereas at non-physiological concentrations (100 nM), it was shortened. The 1 nM effect was due to I_{Kr} inhibition, since patch-clamp recordings of cardiomyocytes showed that E2 reduced only I_{Kr}, but not I_{Ks} nor $I_{Ca,L}$. Higher E2 concentrations affected all tested currents, resulting in APD shortening. Since an oestrogen-receptor inhibitor did not antagonize the E2 effect, a direct, receptor-independent, inhibition of the cardiac I_{Kr} current was proposed.

In a second part, the authors studied the hERG channel expressed in HEK293 cells. They recorded the whole-cell biophysical properties of the suppression of the hERG current upon E2 superfusion. Maximum current was not decreased by E2, but the voltage-dependence of activation was shifted towards depolarized potentials ($\Delta V_{1/2}$: +3–4 mV), suggesting that E2 does not act as a pore blocker, but rather as a gating modifier.

The authors further investigated some of the molecular features of this interaction. Based on the main structural differences between dihydrotestosterone (DHT) and E2 (Fig. 5*A* in Kurokawa *et al.* 2008), they studied the role of the aromatic residues lining the pore of hERG. Tyr652 and Phe656 are known to be crucial for many drug–hERG interactions, and Phe specially for aromatic–aromatic ones (Stansfeld *et al.* 2007). Kurokawa *et al.* observed that only the Phe656 mutation abolished the E2-dependent modulation of hERG. Phe656 is also involved in the binding site of E4031, a potent hERG blocker. Surprisingly, E2 did not attenuate the E4031 block of hERG, as may have been expected if the two molecules would compete for the same site. Proposed explanations point at allosteric modifications of the blocker-binding site. Furthermore, ECG recordings were consistent with the patch-clamp findings, since QTc was also increased in guinea pig hearts when treated with both E4031 and E2, but not when DHT was added to E4031.

The study by Kurokawa *et al.* provides new insights into the possible causes making women more prone to develop di-LQTS. Whereas genomic effects of sex hormones have been previously shown to underlie this difference (Drici *et al.* 1996), this work convincingly describes effects of E2 that are independent of the oestrogen receptor. This new information will have to be taken into account when evaluating the risk of drug-induced TdP in females during the menstrual cycle. Future integration of these risks might one day lead to gender equality, at least in this field.

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